REMARKS

Claims 1, 4, 5, 12-14, 16, 38, 39, and 49 are amended herein; claims 7 and 41 are cancelled herein; and new claims 54 and 55 are presented herein. Upon entry of this amendment, claims 1, 4, 5, 8-14, 16, 29-39, 42-47, and 49-55 are pending.

I. Claim Objections

Claim 1 is objected to for a grammatical error. In the interest of advancing prosecution, claim 1 is amended herein to insert the word "and" after the phrase "botulinum toxin suitable for use in humans".

Claim 6 is objected to for reciting dependency to a cancelled claim. In the interest of advancing prosecution, claim 6 is amended herein to recite dependency on claim 1.

II. Rejection Under 35 U.S.C. 112, ¶ 2

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for reciting the word "comprising" in the phrase "an excipient protein comprising serum albumin." According to the Examiner, the subject phrase fails to particularly point out the composition and subject matter of the invention. Applicants respectfully disagree, but in the interest of advancing prosecution, Applicants respectfully note that the amendment to claim 1 removing the phrase "an excipient protein comprising" renders this rejection moot.

III. Rejection under 35 U.S.C. § 112, ¶ 1- New Matter

A. "Ready-to-Use"

Claims 1, 4-5, 7-14, 16, 29-39, 41-47, and 49-53 are rejected as containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner contends that the term "ready-to-use" recited in independent claims 1 and 16 is not supported in the specification as originally filed.

In determining whether an amendment goes beyond the subject matter of the originally filed application, one must consider the disclosure as a whole and the knowledge possessed by the skilled artisan at the time of filing. *See, e.g., In re Lukach,* 169 USPQ 795,796 (CCPA 1971); *In re Lange,* 209 USPQ 288 (CCPA 1981). It is well settled that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention...the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case of lack of adequate descriptive support...". *Ex parte Parksi,* USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). So long as "a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention a the time of filing, even if every nuance of the claims is not explicitly described in the specification..", the written description requirement is met. *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). Indeed, the subject matter of the claim can be supported in the specification through express, implicit or inherent disclosure. MPEP § 2163.

The Examiner contends that "ready-to-use" is not explicitly or implicitly taught in the specification.[1] Applicants respectfully disagree. First, the "ready-to-use" limitation finds explicit support in the as filed application at page 3, lines 8-10 ("There is therefore a need for a **ready-to-use** liquid formation of botulinum toxin that can be conveniently shipped, stored and used as needed by the clinician. The present invention provides such a formulation." (emphasis added)). Additionally, the "ready-to-use" limitation is implicitly supported in the application as filed, such as at page 3, lines 24-30; page 6, lines 8-13, 15-18; page 13, lines 5-11; page 20, Example 1; page 21, Example 2 and Table 2; and page 22, lines 1-8. In each case, one of skill will recognize that the formulations disclosed are stable and ready-to-use.

The Examiner further contends that "it is not clear if 'ready-to-use' is meant to encompass both the concentrated form and the diluted 'working' preparation or whether it is only meant to encompass the diluted preparation."[2] Applicants respectfully disagree. First, Applicants respectfully note that issues regarding lack of clarity are properly rejected under 35 U.S.C. 112, ¶2, not 35 U.S.C.

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[1] *See* Office Action at page 3, paragraph 2

[2] *Id.*

112, ¶1. Secondly, as readily envisaged by one of skill from the explicit and implicit teaching of the as filed application, the term "ready-to-use" refers to the feature that the present liquid formulations do not require re-constitution from solid, lyophilized botulinum toxin prior to use. *See, e.g.*, specification at page 13, lines 5-11 ("[the present] formulation can be conveniently dispensed to humans or other mammalian species as a pharmaceutical **without further re-constitution** by the physician" (emphasis added)). This "ready-to-use" feature distinguishes the present stable, liquid formulations from the prior art and is advantageous over solid, lyophilized formulation in the clinical setting because it circumvents the possibility of user error when diluting the toxin. *See, e.g.*, page 6, lines 8-13 ("This [present] formulation is advantageous, because... it **reduces the possibility of errors in dilution of the toxin** which could result in overdose" (emphasis added)).

For these reasons, Applicants respectfully assert that the limitation "ready-to-use" does not constitute new matter. However, in the interest of advancing prosecution, the present amendments to claims 1, 12-14, and 16 remove the term "ready-to-use", and renders the rejection on this basis moot.

B. pH "5.6 ± 0.2"

Claim 4 is rejected as containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner contends that the specific pH range "5.6 ± 0.2" recited in the phrase "wherein said buffered pH is pH 5.6 ± 0.2" is not supported in the specification as originally filed. Applicants respectfully disagree.

The specification provides explicit support for the present formulations at a buffered pH range from 5.4 to 5.8, *i.e.* 5.6 ± 0.2. *See*, for example, page 3, lines 26-28 ("According to this general embodiment the toxin is mixed in a buffered liquid to form a liquid formation which has a pH of between 5 and 6, **particularly between about pH 5.4 and pH 5.8**, and preferably about pH 5.5-5.6." (Emphasis added.)) In addition to the explicit support, the claimed pH range of 5.6 ± 0.2 is implicitly supported by the specification's disclosure that the buffered pH range of the presently claimed formulation can be between pH 5 and 6, a range which encompasses 5.6 ± 0.2. In fact, the

Examiner admits that the specification describes the presently claimed formulation at a pH range from 5 to 6.[3] Therefore, from the specification's explicit and implicit disclosure that the present formulations can have a buffered pH ranging from 5.4 to 5.8 or a buffered pH ranging from 5 to 6, one of ordinary skill in the art would readily envisage that Applicants were in possession of the present formulations at a buffered range of 5.6 ± 0.2.

For these reasons, Applicants respectfully assert that a *prima facie* new matter rejection has not been established. However, in the interest of advancing prosecution, dependent claim 4 is amended herein to recite a "pH range between about pH 5.4 and pH 5.8" as explicitly supported in the specification at page 3, lines 26-28. Consistent with this recitation, dependent claim 39 is also amended herein to recite a "pH range between about pH 5.4 and pH 5.8".

IV. Rejection under 35 U.S.C. § 112, ¶ 1- Scope of Enablement

Claims 1, 4, 5, 7-13, 29-39, 41-47, and 49-53 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not teach how to make and use the full scope of the claimed invention. While the Examiner admits that the specification is enabling for a stable liquid botulinum toxin formulation in succinate buffer at pH 5.6 with recombinant human serum albumin, the Examiner contends that specification does not enable one of skill to make and use stable botulinum toxin liquid formulations in any other type of buffer, at any other pH, or with any other excipient protein besides recombinant human serum albumin.[4] Applicants respectfully disagree and for the reasons provided below, Applicants respectfully assert that the full scope of the claimed formulations, as presented herein, is enabled by the specification.

A. *The present invention, drawn to stable, ready-to-use, liquid pharmaceutical formulations of botulinum toxin, is distinguishable from prior art solid, lyophilized formulations of botulinum toxin which require reconstitution prior to administration*

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[3] *See* Office Action at page 4, first paragraph ("The stable botulinum toxin formulation is characterized by a pH between about pH 5 to 6, preferably about pH 5.5-5.6 on page 13 of the specification." (emphasis added))

[4] *See* Office Action at page 4, second full paragraph

As discussed in Section III(A) above, the specification teaches that the claimed liquid formulations of botulinum toxin are distinguishable from prior art solid, lyophilized formulations in that reconstitution of the solid form is not required prior to administration to a patient. This is an advantageous feature to the clinician because the possibility of dilution errors is reduced by circumventing the reconstitution step.

Additionally, the specification teaches that the claimed liquid formulations are more economical and practical for use in a clinical setting, allowing the clinician to administer a dosage from a vial containing the claimed liquid formulation, then store the vial for several weeks, for example, at refrigerator temperatures, and subsequently administer another dose from that same vial without experiencing appreciable loss in toxin potency.[5] In contrast, a clinician is not able to administer multiple doses, in which each dose has approximately the same toxin potency, from a single vial of *reconstituted* solid, lyophilized formulations over a period of several weeks. Thus, after delivering only one dosage, the clinician would discard the vial of reconstituted botulinum toxin because, as discussed in the prior art cited by the Examiner, the potency of botulinum toxin in reconstituted forms of solid, lyophilized formulation is significantly diminished over extended periods of time. *See, e.g.*, specification at page 3, lines 3-7 ("when the reconstituted formulation was stored in a sub-zero freezer at -70°C, it lost about 70% of its potency after two weeks... it is recommended that such compositions not be used later than 4 hours after reconstitution. This can result in a significant waste of drug and cost to the patient." (emphasis added)).

Further, the Examiner acknowledges that reconstituted forms of solid, lyophilized formulations of botulinum toxin cannot be stored for protracted periods of time. *See* Office Action at page 6, first full paragraph in which the Examiner states that "the FDA recommends that liquid preparations of the commercially available lyophilized toxin be discarded after just 4 hours" (emphasis added). Submitted herein as Appendix A, to further corroborate Applicants' assertions that clinicians are not able to administer multiple doses of reconstituted solid, lyophilized

[5] *See* specification, for example, at page 13, lines 5-11 and 16-19

formulations of botulinum toxin, is the current U.S. Food & Drug Administration-approved product insert for BOTOX® Cosmetic which states:

> **BOTOX® COSMETIC is supplied as a single patient use vial.** The product and diluent do not contain a preservative. Once opened and reconstituted it should be stored in a refrigerator (2° to 8°C) and used within four hours. Discard any remaining solution.

B. *The cited prior art discusses instability problems associated with reconstituting solid, lyophilized formulations of botulinum toxin*

In an effort to establish the notion that "stability of botulinum toxins in liquid form is unpredictable",[6] the Examiner cites the teachings of Goodnough *et al.* (Applied and Enviornmental Microbiology, 58(10): 3426-3428 (1992)), Gartlan *et al.* (Otolaryngology-Head and Neck Surgery, 108(2): 135-140 (1993)), and McLellan *et al.* (Toxicon, 34(9): 975-985 (1996)).[7] However, Applicants respectfully point out that these teachings discuss stability problems associated with solid, lyophilized formulations when reconstituted. As discussed above and detailed further below, the presently claimed stable, ready-to-use, liquid pharmaceutical formulations are distinguishable and exhibit superior long term stability in comparison to reconstituted solid, lyophilized formulations described in the cited prior art.

(1) *Goodnough et al. teaches instability problems associated with reconstituting solid, lyophilized botulinum toxin*

The Examiner cites Goodnough *et al.* for the contention that it teaches "that a commercially available lyophilized product, diluted and lyophilized at pH 7.3 in a diluent containing sodium chloride and human serum albumin, is unpredictable in its stability depending on the buffer used to reconstitute the preparation".[8] Applicants agree that Goodnough *et al.* teaches instability problems

[6] *See* Office Action at page 6, first sentence of first full paragraph

[7] *See* Office Action at page 6, first full paragraph- page 7, first paragraph

[8] *See* Office Action at page 6, first full paragraph; emphasis added

associated with *reconstituting* a solid, lyophilized formulation of botulinum, which as discussed above, is distinguishable from the presently claimed stable, ready-to-use, liquid pharmaceutical formulations.

Moreover, Goodnough *et al.* investigates the effect of solution, pH, and excipients on toxin recovery during the lyophilization process. "In this study we found that conditions including the pH and the use of excipients during the lyophilization procedure affect the recovery of toxicity."[9] That is, in Goodnough *et al.*, fixed amounts of botulinum toxin were diluted in the various solutions listed on Table 1 at page 3427, the potency of each toxin solution was determined, the toxin solutions were lyophilized to solid form, the solid, lyophilized toxin was reconstituted in 1mL water or 0.85% saline, and the potency of each reconstituted toxin solution was determined following lyophilization. By evaluating toxin potency before and after lyophilization, the teaching of Goodnough *et al.* is drawn to determining optimal solutions to dilute the toxin in prior to conducting the lyophilization in an effort to maximize the recovery of toxin after lyophilization.

In contrast, the claimed formulations are ready-to-use as a liquid pharmaceutical, and as such, one of skill does not have to necessarily engage in the lyophilization related study taught in Goodnough *et al.* to make and use the claimed stable, ready-to-use liquid pharmaceutical formulation. Accordingly, Applicants respectfully assert that Goodnough *et al.* is not directed to the claimed formulations and therefore, does not support the Examiner's contention of unpredictably in the state of the prior art as it relates to the claimed stable, ready-to-use liquid pharmaceutical formulations.

(2) *Gartlan et al. teaches instability problems associated with reconstituting solid, lyophilized botulinum toxin*

The Examiner cites Gartlan *et al.* for the contention that "the choice of diluent, buffer, pH and storage temperature all have profound effects on the stability of liquid preparations."[10]

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[9] *See* Goodnough *et al.* at page 3426, second paragraph; emphasis added

[10] *See* Office Action at page 6, first full paragraph

However, the teaching of Gartlan *et al.* is directed at *reconstituted* forms of solid, lyophilized botulinum toxin which, as discussed above, is distinguishable from the presently claimed stable, ready-to-use, liquid pharmaceutical formulations. For example, Gartlan *et al.* states that "[w]hen the reconstituted vials of Botox were refrigerated for one week, Scott found that the LD50 doses of gelatin-diluted Botox were 30% to 33% of the LD50 doses of the saline diluted Botox."[11]

Moreover, in contrast to the formulations in Gartlan *et al.*, the claimed stable, ready-to-use, liquid pharmaceutical formulations retain toxin potency for extended periods of time, *i.e.*, at least one year when at temperatures between about 0 and 10°C or at least 6 months when at temperatures between about 10 and 30°C. Gartlan *et al.* evaluated toxin potency of botulinum toxin formulations that were subjected to freezer storage assays, and reported that these formulations exhibited "statistically significant increase in the LD50 compared to controls."[12] Thus, the formulations taught in Gartlan *et al.* do not possess the presently claimed stability features. For all these reasons, Applicants respectfully assert that Gartlan *et al.* is not directed to the claimed formulations and therefore, does not support the Examiner's contention of unpredictably in the state of the prior art as it relates to the claimed stable, ready-to-use liquid pharmaceutical formulations.

(3) *McLellan et al. teaches instability problems associated with reconstituting solid, lyophilized botulinum toxin*

The Examiner cites McLellan *et al.* for the contention that "different formulations of toxin differ in potency as a result of the choice of the diluent used to prepare the clinical preparations and the storage temperature".[13] Again, Applicants respectfully assert that McLellan *et al.* is directed at *reconstituted* forms of solid, lyophilized botulinum toxin which, as discussed above, is distinguishable from the presently claimed stable, ready-to-use, liquid pharmaceutical formulations. For example, McLellan *et al.* teaches that "[t]he diluent buffer used for reconstitution and injection of toxin has been implicated as being responsible for large differences in potency estimates of

[11] *See* Gartlan *et al.* at page 139, first full paragraph; emphasis added

[12] *See* Gartlan *et al.* at page 139, first full paragraph

[13] *See* Office Action at page 6, last sentence- page 7, first sentence

clinical formulations".[14] Even the Examiner's particular citation to the bridging paragraph on pages 979-981 of McLellan *et al.* discusses the stability of solid, lyophilized formulations, not liquid formulations of botulinum toxin. "Formulations of type A botulinum toxin of two representative freeze-dried preparations were stored for 60 days at five different temperatures as indicated in Fig. 4."[15] For these reasons and the reasons already provided above, Applicants respectfully assert that McLellan *et al.* is not directed to the claimed formulations and therefore, does not support the Examiner's contention of unpredictably in the state of the prior art as it relates to the claimed stable, ready-to-use liquid pharmaceutical formulations.

C. *The specification enables the claimed formulations, which require serum albumin*

Contrary to the Examiner's assertion that the claims encompass any excipient protein, the presently claimed formulations require the presence of serum albumin. Thus, the relevant inquiry under the Examiner's scope of enablement rejection with respect to the inclusion of excipient proteins is limited to whether the specification enables one of skill to make and use stable, ready-to-use, liquid pharmaceutical formulations of botulinum toxin that comprise serum albumin. Applicants respectfully assert that the specification provides sufficient guidance to enable one of skill to make and use the claimed formulations, which explicitly require serum albumin.

(1) *The specification provides sufficient guidance on the type and amount of serum albumins to be included in the claimed pharmaceutical formulations*

First, the specification explicitly teaches that the claimed pharmaceutical formulations comprise serum albumin proteins that are non-immunogenic. "Preferably, the excipient protein [*e.g.*, serum albumin] is selected for its ability to be administered to a mammalian subject without provoking an immune response." *See* specification at page 14, lines 19-21. "Such proteins [*e.g.*, serum albumins] will preferably be relatively non-immunogenic to the mammalian species into which the pharmaceutical formulation is to be administered." *See* specification at page 8, lines 5-8.

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[14] *See* McLellan *et al.* at page 976, first paragraph; emphasis added

[15] *See* McLellan *et al.* at page 979, last paragraph; emphasis added

The specification further teaches that the *type* of serum albumin to be selected for inclusion into the claimed pharmaceutical formulations will depend, in part, on the organism treated. "For example, human serum albumin is well-suited for use in pharmaceutical formulations that are administered to humans; conversely, bovine serum albumin might be selected for use in cattle." *See* specification at page 14, lines 21-23.

Additionally, the specification also provides guidance on *how much* serum albumin should be included into the claimed pharmaceutical formulations for treatment in humans without evoking a significant immunological or allergic reaction. "By way of example, in studies carried out in support of the present invention, it has been determined that a concentration of 0.5 mg/mL human serum albumin is sufficient for purposes of formulations containing 5000 U/mL botulinum toxin Type B, while not evoking a significant immunological or allergic reaction in most humans; generally concentrations of between about 0.05 mg and 1 mg per 1000 U botulinum B should provide sufficient protection." *See* specification at page 14, line 28- page 15, line 2. "For example, 'BOTOX®' is stabilized by addition of 0.5 mg albumin per 100 units of toxin activity (PDR)." *See* specification at page 15, lines 4-5.

(2) *The specification sufficiently addresses the Examiner's contentions related to the teaching of Goodnough et al.*

The Examiner cites Goodnough *et al.* for two contentions: first, that "excipient proteins vary in stabilizing effect" and second, that "human serum albumin derived from blood and gelatin, are contraindicated due to the possibility of blood contaminants or pyrogens."[16] With regards to the Examiner's first contention, it is again noted that the claimed formulations are limited to serum albumins and in fact, Goodnough *et al.* teaches that addition of human serum albumin or bovine serum albumin imparts a stabilizing effect (*i.e.*, increases toxin recovery) in reconstituted forms of

[16] *See* Office Action at page 6, first full paragraph

solid, lyophilized botulinum toxin.[17] Regarding the Examiner's second contention regarding possible contamination, the specification specifically teaches, as discussed above, selecting non-immunogenic serum albumins and provides guidance on how one of skill could select appropriate non-immunogenic albumins for inclusion into the claimed pharmaceutical formulations.

Considering that the claimed formulations are limited to serum albumins as the excipient protein and considering that the specification teaches the type as well as the quantity of serum albumins to be included in the claimed formulations, Applicants respectfully request that the scope of enablement rejection, at least with respect to the scope of excipient proteins, be withdrawn.

D. *The claimed formulations are stable throughout the claimed pH range*

The Examiner contends that the specification does not enable one of skill to make and use the claimed formulations at pH values other than pH 5.6. Applicants respectfully disagree. First, the specification explicitly teaches the claimed stable, liquid formulations are characterized as being within the pH range of 5 to 6. "The formulation is characterized by a pH of between about pH 5 and 6, preferably about pH 5.5-5.6, as maintained by appropriate buffering conditions." *See* specification at p. 13, lines 11-13 (emphasis added). Additionally, the specification explicitly teaches one of skill how to make the stable liquid formulations having a pH value ranging between 5 and 6. "According to this general embodiment, the toxin is mixed in a buffer liquid to form a liquid formulation which has a pH of between 5 and 6, particularly between about pH 5,4 and 5.8, and preferably about pH 5.5-5.6." *See* specification at p. 3, lines 26-28 (emphasis added).

Secondly, the working examples in the specification provide sufficient guidance to enable one of skill to make stable, liquid toxin formulations at pH values ranging from 5 to 6. Example 1 illustrates an exemplary claimed liquid toxin formulation having a pH of 5.6, and Table 1 of Example 1 lists the addition of hydrochloric acid "for pH adjustment" to make the exemplary liquid toxin formulation at pH 5.6. Because it is a matter of routine experimentation for one of skill to

[17] *See* Goodnough et al. at page 3427, left column, last paragraph ("Recovery of toxin activity was also increased by the addition of HSA or bovine serum albumin (BSA) as a bulking agent (Table 1).")

adjust the pH of the exemplary formulation from 5.6 to another pH value within 5 to 6 by adding hydrochloric acid, for instance, Applicants assert that specification fully enables one of skill to make the claimed formulations at pH values other than pH 5.6, but within the range of pH 5 to 6.

Thirdly, the specification provides sufficient guidance to enable one of skill how to determine stability of the claimed liquid toxin formulations at pH values ranging from 5 to 6. For instance, Example 2 of the specification provides various tests that can be used to determine whether a particular formulation possesses the stability features presently claimed. One exemplary test, in Example 2 and listed on Tables 2 and 3, measures the pH value of a claimed liquid toxin formulation over prolonged periods of time at 5° and 25°C, respectively. In light of Example 2 which provides sufficient guidance one how one of skill can determine stability of a liquid toxin formulations having pH values ranging from 5 to 6, Applicants assert that specification fully enables one of skill to make and use the presently claimed stable, liquid toxin formulations at pH values ranging from 5 to 6.

The Examiner cites Gartlan *et al.*, particularly page 139, paragraphs 2-7, for the contention that "pH... have profound effects on the stability of liquid preparations."[18] However, close inspection of these cited paragraphs indicate that these passages are drawn to botulinum toxin formulations having a pH value outside the presently claimed pH range of 5 to 6. Specifically, Gartlan *et al.* at page 139, second full paragraph mentions toxin formulations in sodium phosphate buffer at pH 6.2 and toxin formulations in acetate buffer at pH 4.2:

> Schantz and Kautter found that botulinum toxin can be frozen and thawed without appreciable loss of toxicity when buffered in a sodium phosphate solution of pH 6.2. They further demonstrated that its potency can be maintained without significant loss at room temperature for a few days in this pH 6.2 phosphate buffer and for at least 2 years in a pH 4.2 acetate buffer. The disadvantage of using an acetate buffer is that it cannot be frozen after reconstitution without loss of toxicity." (Emphasis added.)

[18] *See* Office Action at page 6, first full paragraph

Contrary to the Examiner's contention, the cited paragraphs in Gartlan *et al.* do not support the notion that pH values alone are critical determinants for maintaining toxin stability in liquid solutions. Furthermore, the toxin formulations taught in the cited paragraphs in Gartlan *et al.* have pH values outside the scope of the presently claimed pH range of 5 to 6.[19]

For all the reasons above, Applicants respectfully assert that the specification provides sufficient guidance on how to make and use stable liquid toxin claimed formulations having a pH value ranging from 5 to 6. Accordingly, Applicants respectfully request that the scope of enablement rejection, at least with respect to the scope of the claimed pH range, be withdrawn.

E. *The claimed formulations are stable throughout the claimed time periods and temperature ranges*

The Examiner contends that "[t]here is no disclosure of stability of the liquid formulation at temperatures other than about 5°C or about 25°C",[20] and further contends that the specification does not enable one of skill to make and use liquid botulinum toxin formulations that are stable for at least two years at "about 0 and 20 degrees centigrade."[21] While the Examiner admits that the specification enables a liquid botulinum toxin formulation that is stable for at least two years at 5°C or for at least six months at 25°C,[22] it appears that the Examiner is requiring the specification to explicitly demonstrate stability of the claimed formulations at every degree centigrade within the claimed temperature range of 0-10°C and 10-30°C. "There is no disclosure of stability of the liquid formulation at temperatures other than about 5°C or about 25°C."[23] "[T]he specification fails to teach how long the liquid preparations may be stored at temperatures other than about 5°C and about

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[19] *See* also Gartlan *et al.* at page 139, sixth full paragraph ("Considering Schantz and Kautter's work, botulinum toxin appears to be quite stable at room temperature when diluted in a phosphate buffer at pH 6.2." (emphasis added)).

[20] *See* Office Action at page 7, second full paragraph

[21] *See* Office Action at page 4, second full paragraph- page 5, first paragraph

[22] *See* Office Action at page 4, second full paragraph- page 5, first paragraph

[23] *See* Office Action at page 7, second full paragraph

25°C".[24] Applicants respectfully disagree and assert that the specification provides sufficient guidance for one of skill to make and use liquid formulations that are stable over the claimed time and temperature ranges.

First, the specification teaches that the claimed formulations "are stable in liquid form during storage for protracted periods of time (1 year or longer) at standard refrigerator temperatures (approximately 4±2°C, or about 2-8°C, or, more generally, ranging from about 0-10°C). In a related aspect, the formulations are stable in liquid form during storage at 'room temperature' (about 25°, or more generally in the range of 10-30°) for at least six months." *See* specification at page 3, lines 14-20. Thus, the specification enables one of skill to make and use the claimed formulations having the claimed stability features.

Secondly, the specification teaches one of skill representative assays that can be used to determine whether the practiced formulations possess the claimed stability features (*i.e.*, stable as a liquid when stored for at least one year at between about 0 and 10°C, or stable for at least 6 months between about 10 and 30°C). For example, the specification teaches that stability of the claimed formulations can be readily determined, for example, through evaluating toxin potency in a mouse LD_{50} assay of formulations stored over time, as exemplified in Example 2.[25] Other methods taught in the specification for determining stability of the claimed formulations include performing pH assays and colorimetric and visual assessments of the formulations over time.

Because the specification teaches one of skill how to make and use the claimed stable formulations and how to assess whether a practiced formulation has the claimed stability features, Applicants respectfully assert that the specification enables stable, liquid formulations over the claimed time and temperature ranges. However, in the interest of advancing prosecution, claim 1 and dependent claim 5 is amended herein to recite "wherein the formulation is stable as a liquid

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[24] *See* Office Action at page 8, first paragraph

[25] *See* specification at page 13, line 30- page 14, line 2 ("The final product can be stored as a liquid for at least one year and preferably more than two years at 0-10°C without significant loss of biological potency, as evidence by <20% loss of potency in the mouse LD_{50} test (Example 2).")

when stored for at least one year at a temperature of about 5 degrees centigrade". Support for the term "about 5 degrees centigrade" is provided in the specification, for example, at page 13, lines 5-9 ("at 'refrigerator' temperatures (5±3°C, or more specifically, about 4±2°C, or more generally, 0-10°C). Accordingly, Applicants respectfully request that the scope of enablement rejection, at least with respect to the scope of the claimed stability features (*i.e.*, time and temperature ranges recited in claim 1), be withdrawn.

F. *The claimed formulations comprising the claimed buffering components are stable*

The Examiner alleges that the specification is only enabled for the liquid formulation of Example 1 comprising succinate buffer.[26] Applicants respectfully disagree and assert that the specification enables a variety of buffering components for use in the claimed stable liquid toxin formulations, specifically phosphate, phosphate-citrate, and succinate buffers. First, the specification explicitly teaches that succinate and phosphate buffers are "particularly suitable" buffers which "will not adversely affect the stability of the complex, and which supports a stable pH range between about pH 5 and pH 6." *See* specification at page 14, lines 3-6. Additionally, the specification teaches that phosphate, phosphate-citrate, and succinate buffers are "physiological buffers that are considered safe for injection into mammalian tissue, particularly into humans." *See* specification at page 4, lines 13-16.

Therefore, in light of the exemplary citations of the specification provided above, Applicants respectfully assert that the specification provides sufficient guidance for one of skill to make and use the claimed formulations, and specifically those having phosphate, phosphate-citrate, or succinate buffering components. However, in the interest of advancing prosecution, claim 1 is amended herein to require the presence of succinate buffer. Thus, the Examiner's assertion that the claimed formulations encompass all "different" buffering components is rendered moot in light of the present

[26] *See* Office Action at page 7, second full paragraph ("Applicant's disclosure is limited to the formulation described in Example 1 and Table 1 on pages 20-21, which is a liquid formulation prepared in succinate buffer at pH 5.6 with recombinant human serum albumin as an excipient protein which was stable at 5°C for 30 months and was stable at about 25°C for 6 months")

amendments.[27] Accordingly, Applicants respectfully request that the scope of enablement rejection, at least with respect to the scope of the claimed buffering components, be withdrawn.

F. *In sum, one of skill can make and use the full scope of the claimed formulations*

As discussed above, the specification provides sufficient guidance for one of skill to make and use the claimed ready-to-use, stable, liquid pharmaceutical formulations. Specifically, the specification enables the inclusion of serum album and the inclusion of phosphate buffer, phosphate-citrate buffer, or succinate buffer in the claimed formulations. Additionally, the specification teaches one of skill how to make and use formulations that are stable throughout the claimed pH range of 5 to 6, and how to make, use, and determine whether a practiced formulation is stable throughout the claimed time and temperature ranges (*i.e.*, stable as a liquid when stored for at least one year at between about 0 and 10°C, or stable for at least 6 months between about 10 and 30°C).

Also discussed above are the numerous distinctions between the presently claimed stable, ready-to-use, liquid pharmaceutical formulations, and the prior art solid, lyophilized formulations which require reconstitution prior to administration. Because all the prior art cited by the Examiner is drawn to reconstituted lyophilized botulinum toxin, Applicants respectfully assert that the cited prior art does not support the Examiner's contention of unpredictably in the state of the prior art as it relates to the claimed stable, ready-to-use liquid pharmaceutical formulations. For all these reasons, Applicants respectfully request withdrawal of the scope of enablement rejection.

[27] *See* Office Action at page 7, last paragraph ("Because the invention encompasses liquid pharmaceutical compositions of botulinum toxin with different buffering components, different pHs, and different excipient proteins...)

CONCLUSION

In light of the remarks set forth herein, Applicants believe that the present application is in condition for allowance. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Please charge any fee due in connection with this submission to Deposit Account No. 23-2415. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 31242.701.201).

Respectfully submitted,

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